Genetic architecture of dystonia

Groen, Justus

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
A NEW FAMILIAL SYNDROME WITH DYSTONIA AND LOWER LIMB ACTION MYOCLONUS

Justus L. Groen, Anne-Fleur van Rootselaar, Sandra M.A. van der Salm, Bas R. Bloem & Marina A.J. Tijssen.

ABSTRACT

Background: Myoclonus Dystonia (M-D) is genetic and clinically heterogeneous. Identification and description of rare M-D syndromes may contribute to gene identification. Results: Here, we describe a new, autosomal dominant M-D syndrome in a three generation pedigree showing anticipation. Patients have progressive action-induced multifocal dystonia and generalized myoclonus. A remarkable feature of the syndrome is action myoclonus in lower extremities triggered by upright posture, causing instability. Electrophysiological characterisation shows a 12 Hz peak in the EMG autospectrum and corticomuscular and intermuscular coherences. Conclusion: A new familial M-D syndrome with progressive action myoclonus and dystonia.
INTRODUCTION

Familial Myoclonus-Dystonia (M-D) is characterized by dystonia and myoclonus frequently affecting the upper body, a young age at onset and a benign course.\textsuperscript{1,2} Mutations in the DYT11 gene \textit{SGCE} \textsuperscript{3}(OMIM 159 900) are often identified in familial M-D.\textsuperscript{4,5} In DYT11 M-D families psychiatric and cognitive abnormalities\textsuperscript{6-8}, tremor\textsuperscript{9}, epilepsy,\textsuperscript{10} and mental retardation\textsuperscript{11} have been described. Genetic heterogeneity of the M-D phenotype is shown with genetic linkage to the DYT15 locus on 18p11 (OMIM 607488)\textsuperscript{12,13}.

Here, we describe a new M-D syndrome that is different from described M-D pedigrees because of progressive myoclonic jerks and dystonia, action induced lower limb myoclonus, and anticipation. For future genetic research, it is of importance to describe and cluster rare phenotypic identical syndromes.

METHODS

Five affected family members were identified in a 16 member family spanning three generations (Figure 1). Eight family members underwent medical history taking, neurological examination, and rating of dystonia and myoclonus (Toronto Spasmodic Torticollis Rating Scale, Severity part (TWSTRS-S)\textsuperscript{14} and Unified Myoclonus Rating Scale (UMRS) sections 2-5\textsuperscript{15}). Assessments were videotaped.

![Figure 1. Pedigree of described family](image)

\textit{Electrophysiology}

Electrophysiological studies included multichannel surface electromyography (EMG) combined with electroencephalography (EEG), measurement of somatosensory evoked potentials (SSEP) and eye movement recordings. (Textbox 1)
Textbox 1. Methods of electrophysiological studies performed in affected family members.

**EEG and EMG recordings and coherence analysis (III:2, 3, 6)** – EEG was recorded from the scalp using Ag/AgCl electrodes, applied according to the international 10-20 system (Brainlab; OSG bvba, Rumst, Belgium). Surface EMG, using Ag/AgCl electrodes placed 3 cm apart over the muscle bellies, was recorded from the six to eight muscles that were clinically most affected (see results section). The sample frequency was 1,000 Hz and data was high pass filtered at 0.005 Hz. In addition, time-locked video was registered. Recordings were made in the supine position – at rest, with arms and fingers extended, when lifting the right leg, and when lifting the left leg – and during stance. For every condition, at least three minutes of artifact free data was collected. Offline processing was performed using Brain Vision Analyzer software (Brain Products GmbH, München, Germany). Bipolar derivations of EEG and EMG were calculated. EEG and EMG were high passed filtered at 2 Hz and 10 Hz respectively (48 dB/octave) and the EMG was rectified. The duration and amplitude of 10 consecutive bursts was measured per condition in a representative piece of data. Subsequently, corticomuscular and intermuscular coherence measures were calculated. For every condition, a run of at least 180 seconds was analyzed per subject. A Fourier transformation of disjoint sections of 1,024 data points was performed using **MATLAB** (The Mathworks, Cambridge, UK) and **Neurospec** (www.neurospec.org), applying a 50-Hz notch filter and a Hanning window. The sections were averaged to obtain the frequency autospectra of signal a \((faa[\lambda])\) and signal b \((fbb[\lambda])\), representing EEG and/or EMG, and their cross-spectrum \((fab[\lambda])\). Coherence, a measure of the correlation between the signals in frequency space, was estimated between EMG and contralateral and ipsilateral EEG, and between EMG and EMG. Coherence is defined by \(|Rab(\lambda)|^2 = |fab(\lambda)|^2 / faa(\lambda)fbb(\lambda)\) and ranges from 0 (no correlation) to 1 (perfect correlation). Cumulant density estimates were calculated as the inverse Fourier transform of the crossspectra. Phase, \(\phi\), defined as the argument of the cross spectrum: \(\phi_{ab}(\lambda) = \arg(fab[\lambda])\), was also calculated. Coherence was considered to be significant if it exceeded the 95% confidence level.

**SSEP recordings and analysis (our lab III:2, 6; other center III:3)** – SSEPs in III:2 and III:6 were recorded on a Medelec Synergy system (Oxford Instruments Medical Limited, Old Woking, Surrey, UK). Electrodes (Ag/AgCl) were placed at Erb’s point, cervical spine, A1, A2, and 1.5 cm posterior to C3 and C4 (C3’ and C4’) according to the International 10–20 System. Filter band pass was 20 Hz to 2 kHz. When stimulating the right median nerve, channels were referenced to A1, and when stimulating the left median nerve, channels were referenced to A2. No electronic smoothing was used. The median nerve was stimulated at both wrists, one at the time, by a bipolar surface electrode with stimulus duration of 0.2 ms and a stimulus strength set to produce a small thumb twitch. Per wrist, 2 x 512 responses (rejected responses not included) acquired at 4.1 Hz were averaged and superimposed, as were 2 x 300 responses acquired at 1.1 Hz. Short latency potentials were determined. A giant SSEP was considered to be present in case P25-N35 extended 5μV and reached 5x the amplitude of the N20 (our laboratory standard). SSEP in patient III:2 was recorded elsewhere and revised.

**Eye movement recordings and analysis (III:2, 3, 6)** – Visual inspection of eye movements was carried out preceding the eye movement recordings. Movements of the right eye were measured with an electromagnetic eye recording method (double magnetic induction method, DMI). Participants were seated in a custom made chair with their heads positioned in a homogeneous alternating primary magnetic field with constant amplitude, and stabilized by a chin rest and a head tie. A gold plated metallic ring, placed onto the eye after desensitization...
with 0.4% solution of Oxybuprocaine hydro-chloride, generated a secondary magnetic field related to the rotation of the ring. The field strength was recorded by a detection coil placed in front of the eye. Horizontal and vertical eye positions were derived applying the phase-locked amplitude technique. The stimulus was a red laser dot presented on a translucent screen at 1.14 m from the eyes in a faintly illuminated room. Data were digitally stored in the computer at 1,000 Hz sampling rate and analyzed offline. Smooth pursuit eye movements (SPEM), saccades, and spontaneous nystagmus in darkness with and without hyperventilation (HV) were evaluated. Participants performed trials of horizontal smooth triangular pursuit (10°/sec) and vertical smooth triangular pursuit (10°/sec), both lasting 60 sec. Fifty saccades were performed in the horizontal and also in the vertical direction. Amplitudes ranged from 2° to 20°, were randomized, and did not exceed -10° and +10° from gaze straight ahead. Duration between trials was varied pseudorandomly between 1.5 and 3 sec. Nystagmus was recorded in darkness with the eyes open, 10 sec before, 60 sec during, and 30 sec after HV.

Laboratory investigations and genetic testing are specified in the Results section. Investigations were performed with informed consent.

RESULTS

Disease onset was spasmodic dysphonia at age 62 years in patient II:2; writer’s cramp at 12 years (III:2), 15 years (III:3) and 37 years (III:6) and dystonia of the feet at age 4 in patient IV:6 (Table 1A). Patient III:2 and III:3 are described below, other patients in Textbox 2.

Table 1. Clinical and electrophysiologic characteristics of affected family members. Patient numbers correspond to pedigree position. f=female, m=male, LE=lower extremities, UE=upper extremities, SSEP=somatosensory evoked potentials, IM=intermuscular; CM=cortico-muscular.

A. Overview of clinical characteristics of the five affected family members

<table>
<thead>
<tr>
<th>Pedigree</th>
<th>Age</th>
<th>Sex</th>
<th>Disease duration</th>
<th>Dystonia</th>
<th>Myoclonus</th>
<th>Action induced lower limb myoclonus</th>
<th>Alcohol responsive</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-2</td>
<td>84y</td>
<td>f</td>
<td>22y</td>
<td>voice, neck, UE</td>
<td>voice, LE</td>
<td>yes</td>
<td>unknown</td>
</tr>
<tr>
<td>III-2</td>
<td>52y</td>
<td>f</td>
<td>37y</td>
<td>neck</td>
<td>generalized</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>III-3</td>
<td>51y</td>
<td>f</td>
<td>39y</td>
<td>UE, LE</td>
<td>generalized</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>III-6</td>
<td>43y</td>
<td>f</td>
<td>6y</td>
<td>voice, neck, UE</td>
<td>face, hands</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>IV-6</td>
<td>9y</td>
<td>m</td>
<td>5y</td>
<td>UE, trunk, LE</td>
<td>LE</td>
<td>no</td>
<td>unknown</td>
</tr>
</tbody>
</table>
B. Summary of the neurophysiologic findings.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Condition</th>
<th>EMG</th>
<th>Autospectra</th>
<th>Coherence</th>
<th>SSEP</th>
<th>Eye movements</th>
</tr>
</thead>
<tbody>
<tr>
<td>III-2</td>
<td>rest</td>
<td>50-200msec, semi-rhythmic</td>
<td>4Hz</td>
<td>N35: 5.2uV</td>
<td>Supp. Fig. 3B</td>
<td></td>
</tr>
<tr>
<td>action</td>
<td>amplitudes&gt;&gt;</td>
<td>4Hz</td>
<td>4Hz: IM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standing</td>
<td>amplitudes&gt;&gt;</td>
<td>5Hz (10Hz)</td>
<td>5Hz, 10Hz: IM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-3</td>
<td>rest</td>
<td>50-100msec, semi-rhythmic</td>
<td>5Hz</td>
<td>N35: 7uV</td>
<td>normal</td>
<td></td>
</tr>
<tr>
<td>action</td>
<td>amplitudes&gt;&gt;</td>
<td>8Hz (4Hz)</td>
<td>4Hz, 8Hz, 11Hz: IM, CM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standing</td>
<td>amplitudes&gt;&gt;</td>
<td>12Hz</td>
<td>8Hz, 12Hz: IM, CM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-6</td>
<td>rest</td>
<td>no jerks</td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>action</td>
<td>50-100ms, irregular</td>
<td>8Hz, 12Hz</td>
<td>no peaks</td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>standing</td>
<td>amplitudes&gt;&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Index patient (III:3) – This 51 year old woman developed action induced irregular jerks of both hands and writer’s cramp of her right hand, at age 12 years. The jerky movements gradually expanded to other body regions. At the age of 40 years she developed cervical dystonia. Currently, progressive gait difficulties (described as ‘stiffness’ and ‘a high tension in the legs’) force her to use a wheelchair. Alcohol eases the jerks, clonazepam and sodium valproate did not. Currently she has little beneficial effect of diazepam (5 mg dd). Her medical history revealed panic attacks, depression and hyperventilation syndrome. Examination showed continuous jerks of the hands, neck, face and voice at rest (UMRS-2: 33/128) that increased on action and were not stimulus sensitive (UMRS-4: 60/160; UMRS-5: 9/20). She had continuous jerky activity in the lower limbs and trunk, worsening with longer duration of standing. She had a cervical dystonia (TWSTRS-S 12/35), a light rotation of the trunk and complex writer’s cramp. While lifting the leg in supine position, a dystonic posturing of her right foot developed (Video). EMG showed semi-rhythmical bursts of 50-100 ms, increasing in amplitude and duration in action (Figure 2).

During dystonic posturing of the right foot a frequency peak at 8 Hz and at 4 Hz was seen with intermuscular and corticomuscular coherence peaks around 4 Hz with a cortical drive (Figure 3A). While standing, without dystonic posturing of the foot, the peak in autospectra of leg muscles shifted to 12 Hz, with intermuscular and corticomuscular coherences in the same frequency band without a cortical drive (Figure 3B). SSEP recordings showed a P25-N35 complex of 7 μV, with a normal N20 potential, not reaching the criteria of a giant SSEP. No C-response was present. Electromagnetic eye recording revealed no abnormalities.

The index patient’s oldest sister (III:2) – This 52 year old woman had writer’s cramp since age 15 years. From age 40 years, restlessness of the face, voice, neck and hands developed,
A new familial syndrome with dystonia and lower limb action myoclonus

Figure 2. Electromyography of patient III-3. EMG shows short bursts at a frequency around 5Hz (10Hz) while seated (rest, A; two scales are shown). EMG when lifting the right leg, inducing dystonic posturing of the foot (extension, B1, see also VIDEO). When resting the leg, muscle activity remains present in the right m. tibialis anterior and right m. gastrocnemius for a short period of time (B2). With standing the bursts increase in all leg muscles (stance, C; two scales are shown).

progressive over the years. At presentation, her major complaints were these jerky movements and a feeling of ‘shaking legs’ with standing and walking. Alcohol had a highly positive effect on the jerks; clonazepam and levetiracetam did not improve the symptoms. Medical history included panic attacks, hyperventilation, and Wolf-Parkinson-White syndrome. At neurological examination a tremulous, dystonic voice and a prominent cervical dystonia (TWSTRS-S: 16/35) were present. She had myoclonic jerks of the face musculature, neck, arms and hands during rest, increasing in severity with action (UMRS-2: 37/128). On standing, a high frequency myoclonus of both lower extremities developed, preserved during walking (UMRS-4: 51/160;
Figure 3. Coherence analysis of dystonic and myoclonic movements in patient III-3.
Coherence analysis between right tibialis anterior muscle and central motor areas in patient III-3: during (A) dystonic posturing of the right foot and during (B) standing, inducing tremulousness and an unsteady feeling. Note the shift in peak frequency in the autospectrum of the right tibial anterior muscle between A and B, as well as the different coherence peaks between conditions (the dashed line is the 95% confidence interval). Also note the difference in phase, showing an upward slope in A, consistent with a cortical drive, and a downward slope in B, in line with afferent cortical input (the thin lines indicate the 95% confidence interval).
A new familial syndrome with dystonia and lower limb action myoclonus

Figure 4. Somatosensory evoked potential (patient III-2). When stimulating the left median nerve at the wrist, an enhanced cortical P25-N35 potentialis revealed over the right hemisphere (C4') indicating some enhancement of cortical excitability

UMRS-5: 14/20) (Video). The EMG-EEG registration revealed semi-rhythmical or irregular bursts of 50-200 ms in all recorded muscles with a 4-5 Hz peak in the auto-spectra (Table 1B). The head electrodes revealed similar burst-like activity recorded from the head musculature, obscuring EEG activity. Strong coherences around 5 and 10 Hz were found between neck muscles and EEG (head muscles). The criteria of a giant SSEP were not reached (Figure 4).

Eye movement recordings showed macrosquare-wave jerks during fixation and smooth pursuit eye movements (SPEM). On the hyperventilation challenge in a dark environment a downbeat nystagmus developed. (Figure 5)
**Figure 5.** Electromagnetic eye movement recordings in patient III-2. The horizontal eye position of the right eye (H OD) and the vertical eye position of the right eye (V OD) are shown against the target position. Upper panel (A) shows an upward drift with downbeat nystagmus (V OD) during hyperventilation in darkness. Lower panel (B) shows the macrosquare-wave jerks (H OD) during eye fixation after performing saccades.

**Patient II:2** – The 84 years old mother of the index patient has a dystonic and trembling voice since she was 62 years old. In retrospect she recalls periods of a painful neck, progressive in frequency over time from age 40 years. Gradually myoclonic jerks of her right arm, voice, face and neck developed, worsening with stress. She noticed flexion of her 3rd finger with writing from the age of 50 years. She also complains of trembling and instability of the legs with standing and walking. No information concerning the alcohol responsiveness is available. As medication, natrium valproate was tried without any benefit. Medical history reveals a slightly decreased hearing, cataract, cardiovascular problems and mamma carcinoma. At neurological examination she has dysphonia with intermittent myoclonus of vocal cords interrupting speech. Neck, face and the left arm show continuing short jerks (UMRS-2:21/128). A mild dystonia of neck (TWSTRS-motor score 9/35) and a jerky writer’s cramp with mirror movements is present (UMRS-5: 7/20). While standing and walking, exacerbation of the jerky movements and tremulousness of the legs are observed. (UMRS-4: 34/160) No neurophysiologic examination was performed.

**Patient III:6** – The youngest sister of the index-patient is a 43 year old female with dystonia since she was 37 years old. The first symptom was writer’s cramp, followed by dystonia of voice, neck and toes. At age 40 she notices progressive restlessness of the hands and twitchy movements of the facial musculature. Fatigue and stress worsen the complaints. Speech is hampered and with walking she notices stiffness and an unstable pattern. Alcohol has positive effect on all symptoms. There is some benefit on the myoclonus with temazepam. Her medical history reveals a pneumothorax, pancreatitis due to cholecystolithiasis and multiple abdominal surgical procedures related to this event. There is no history of previous neurological or psychiatric complaints. Current medication is temazepam, omeprazole and pancreas enzyme supplements. She is married and has an unaffected daughter (age 13) and an affected son (age 9) described below (Patient IV: 1). On examination she has a torticollis (TWSTRS-M 8/35), mild dysphonia and writer’s cramp with mirror movements. In rest she shows continuing myoclonic activity of face and hands (UMRS-2: 25/128), worsening with isometric postures (extension of arms or legs) and action (UMRS-4:36/160; UMRS-5: 4/20). EMG is recorded from the SCM R/L, biceps brachii muscles bilaterally, right and left wrist extensor muscles, vastus med R and Tib ant R during rest, extension of the arms, and stance. The EMG registration reveals bursts, mainly in activated muscles that are sometimes almost rhythmical, and have a variable burst length of 40-150ms. The autospectra show sometimes a peak around 12 or 8 Hz, but this is not a consistent finding. Also, no consistent intermuscular coherence or corticomuscular coherence are found. Eye movements were normal. SSEP recordings did not indicate increased cortical excitability.

**Patient IV:6** – The 9 year old son of patient III:6 has mild dystonia since age 4, with endorotation of both feet during walking. Gradually, clumsiness was noted, reflected in falling, and eye-hand coordination problems. Writer’s cramp was present at age 5 years. Also, a progressive restlessness of all extremities and trunk is invalidating in daily life. In school he has problems with learning and reading. His medical history showed a relapsing occurrence of upper airway infections, possibly induced by choking, and problems with falling asleep. Neurological examination shows a slight dystonia of trunk. Restlessness and mild continuing myoclonic activity in arms and legs is seen (UMRS-2: 22/128), exaggerated with maintaining isometric postures and action (UMRS-4: 58/160, UMRS-5: 3/20). While sitting up straight he has intermitted, irregular jerky movements of the trunk, clinically interpreted as negative
myoclonus of the trunk. To avoid this symptom he curves his back, or pulls up his knees to the chest, so decreasing tonic activity in his back muscles. Polymyography of trunk and limb muscles was limited as it was difficult to study him for a prolonged period. During the short registrations we were unable to record the clinically obvious myoclonic bursts.

Table 2. The diagnostic tests performed in patient III-6 and III-3 (†) to exclude known causes of myoclonus-dystonia syndromes.

* Including copy number variation.

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Test</th>
<th>Laboratory</th>
<th>MRI/CT</th>
<th>Biopsy#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonus-Dystonia</td>
<td>SGCE*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>Mt-DNA sequencing</td>
<td>normal BG</td>
<td>no mitochondrial myopathy</td>
<td></td>
</tr>
<tr>
<td>Myoclonic epilepsy and Red Ragged Fibres</td>
<td>MERRF</td>
<td>intensities on MRI</td>
<td>Gomori normal</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke pyruvate dehydrogenase complex deficiency</td>
<td>MELAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial myopathy, encephalopathy, lactic acidosis, stroke pyruvate dehydrogenase complex deficiency</td>
<td>Leigh/NARP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar atrophy</td>
<td>SCA</td>
<td>slight cerebellar atrophy (III:3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>TSH</td>
<td>no accumulation on MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metal metabolic disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson's disease, aceruloplasmaemia</td>
<td>serum copper, ceruloplasmine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neuroacantocytosis</td>
<td>acantocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>neuroferritinopathy</td>
<td>serum ferritin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>haemochromatosis</td>
<td>serum iron, transferrin saturation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pantothenate kinase-associated neurodegeneration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>α-fetoprotein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism defects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopa-responsive dystonia</td>
<td>biopterines, neopterines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cerebral glucose transporter deficiency</td>
<td>GLUT1/SLC2A1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Laboratory investigations**

Additional tests were performed (Table 2) revealing normal levels of ceruloplasmin, Copper, acanthocytes, TSH, alpha-1-fetoproteins, lactate, CK and pyruvate (III-3, III-6) Genetic testing for DYT11 (including gene dosage analysis), DYT1, DYT6, spinocerebellar ataxia (SCA) subtypes 1,2,3,6,7,14,17, POLG1 sequence and trinucleotide repeats, MERRF, MELAS, Leigh/NARP and GLUT1 (in patient III-3) were negative. No mtDNA depletion, mutations or deletions were found and enzymhistochemical tests and electromicroscopic analysis of the biopsy did not provide any insight (muscle biopsy from patient III:3).

**Imaging**

Computed tomography showed mild cortical and cerebellar atrophy in III-3. Magnetic resonance images of the brain in III-2 and III-6 were normal.

**DISCUSSION**

In this three generation pedigree, five members suffer from an M-D plus syndrome. Features compatible with the known M-D phenotype are cervical and axial dystonia at rest, writer’s cramp and action-induced foot dystonia with walking, myoclonic jerks in legs and arms, increasing with action, a positive effect of alcohol on the jerks, and complaints of hyperventilation or panic attacks. However, new interesting and prominent features in this pedigree are the high frequency continuous myoclonus in the legs while standing, causing unsteadiness, the progression of symptoms and genetic anticipation.

Two familial M-D syndromes have been classified as DYT11 and DYT15. Both syndromes are phenotypical similar showing predominant myoclonus of upper body and mild dystonia. The inheritance pattern of our M-D pedigree does not fit the maternal imprinting of SGCE. Moreover, mutations and dosage variants in the SGCE gene were excluded. AD inheritance without maternal imprinting was also seen in the DYT15 M-D family12, however the action induced lower limb myoclonus and progression of symptoms is not described in DYT15 M-D. Anticipation has not previously been described in any M-D pedigree.

The upper body myoclonus was characterized by semi-rhythmical EMG bursts of 40-200 ms during rest. The dystonia in our patients was characterized by corticomuscular and intermuscular coherences around 4 Hz (III:2; III:3) and a cortical drive related to dystonic posturing of the foot (III:3; Figure 3A). Coherences in the 4-8 Hz band have previously been described in M-D18 and late onset idiopathic dystonia.19

While standing, high frequency myoclonic jerks appear in the legs. Intermuscular and corticomuscular coherences around 12 Hz are present in the most severely affected patient (III:3; Figure 3B). The phase differences suggest an afferent (sensory) cortical input. The posture dependent myoclonus resembles the previously described
‘slowly progressive orthostatic myoclonus’ seen in 15 elderly with gait decline.\textsuperscript{20} In 9 of these 15 patients, myoclonus was secondary to neurodegenerative (7/9) or systemic (2/9) diseases. A similar type of lower limb action myoclonus is reported as a rare cause for unsteadiness in Parkinson’s disease patients, showing irregular and brief bursts (9–15Hz, 30-70 ms) in the upright position.\textsuperscript{21} It has never been described as a symptom in a familial syndrome.

Eye movement recordings showed macrosquare-wave jerks during fixation and smooth pursuit combined with an upward drift with downbeat nystagmus on hyperventilation challenge in darkness (III:2; Figure 5), suggestive for cerebellar pathology.\textsuperscript{22,23} No cerebellar signs were noted at clinical examination and only patient III:3 showed mild cerebellar atrophy on the MRI. Interestingly, cerebellar abnormalities have been implicated in dystonia\textsuperscript{24-27} and abnormal functional activity in the cerebellum is associated with myoclonus, especially cortical myoclonus.\textsuperscript{28}

SSEP (Figure 4) showed an intermediate enlarged cortical potential in patients III:2 and III:3 indicating cortical involvement. Intermediate enlarged P25-N35 complexes have been described in dystonia and myoclonus,\textsuperscript{29} possibly indicating secondary changes of the cortical areas resulting from basal ganglia pathology.

The combination of action-induced dystonia, severe lower limb myoclonus and progression of symptoms, is clinically not compatible with the known M-D phenotype. The electrophysiological assessment suggests a subcortical origin with possible cerebellar involvement in this pedigree. Mutation analysis in families by exome\textsuperscript{30,31} or even whole genome\textsuperscript{32} sequencing is now available, using affected individuals from independent kindreds. Only with the identification and careful description of rare features and the definition of syndromes, gene discovery is feasible.

**ACKNOWLEDGEMENTS**

We are grateful to all family members for their kind cooperation. We thank Thijs Boerée for his technical support, Dr. Lo Bour for the eye movement registration and Dr. Hans Speelman for critically reading the manuscript.

**Supplementary video can be viewed online:** http://www.movementdisorders.org/publications/journal.php

**Segment 1:** Patient III-3: myoclonus and dystonia in upper extremities upon action; **Segment 2:** Patient III-3: dystonic inversion of the right foot in extension (with EMG recordings in right leg, for EMG see Supp.Fig. 2B); **Segment 3:** Patient III-3: high-frequency myoclonus upon standing (with EMG recordings of right leg, for EMG see Supp.Fig. 2C); **Segment 4:** Patient III-2: patient is standing, jerky movements, especially in the upper body are profound. Also cervical dystonia is shown. **Segment 5:** Patient III-2: myoclonic jerks and dystonia in upper extremities upon action, more severe in the right arm;
REFERENCES


